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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/766,948	01/30/2004	Helena Gyback	085747-0315	2491
54080	7590	03/03/2006	EXAMINER	
BIRCH, STEWART, KOLASCH & BIRCH, LLP P.O. BOX 747 8110 GATEHOUSE ROAD, SUITE 500 EAST FALLS CHURCH, VA 22040-0747			TUCKER, ZACHARY C	
		ART UNIT	PAPER NUMBER	
			1624	

DATE MAILED: 03/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/766,948	GYBACK ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Zachary C. Tucker	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 22 December 2005.
- 2a) This action is FINAL.                    2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 1-28 is/are pending in the application.
- 4a) Of the above claim(s) 14-28 is/are withdrawn from consideration.
- 5) Claim(s) \_\_\_\_\_ is/are allowed.
- 6) Claim(s) 1-13 is/are rejected.
- 7) Claim(s) \_\_\_\_\_ is/are objected to.
- 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All    b) Some \* c) None of:
1. Certified copies of the priority documents have been received.
  2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- 1) Notice of References Cited (PTO-892)
- 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_.
- 4) Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.
- 5) Notice of Informal Patent Application (PTO-152)
- 6) Other: \_\_\_\_\_.

## DETAILED ACTION

### ***Requirement for Restriction***

A Requirement for Restriction in the instant application was mailed 22 November 2005. Applicant's election with traverse of the invention of Group I, chemical compounds of formula I, in the reply filed on 22 December 2005 is acknowledged. The traversal is on the ground that all of the claims recite a compound of formula I. This is not found persuasive because restrictions between products, processes of using the products and processes of making the products are proper, so long as the conditions addressed in MPEP § 806.05(h) and (f) are satisfied. How these conditions are satisfied with respect to the instant claims is explained in the Requirement for Restriction letter. Applicants' counsel has not specifically taken issue any point raised in the restriction letter.

Applicants further argue that no serious search burden exists. According to the MPEP §803, "...a serious burden on the examiner may be *prima facie* shown if the examiner shows by appropriate explanation of separate classification, or separate status in the art, or a different field of search as defined in MPEP § 808.02. That *prima facie* showing may be rebutted by appropriate showings or evidence by the applicant." Applicant has made no rebuttal of the examiner's showing of separate classification and separate status in the art. Thus, a serious burden has been established.

The requirement is still deemed proper and is therefore made FINAL.

When Group I is deemed to be in condition for allowance, the subject matter of withdrawn Groups II-IV will be rejoined therewith and the Requirement for Restriction

between the Groups withdrawn, so long as the withdrawn claims are commensurate in scope with the allowable subject matter.

At this time, the elected Group is not in condition for allowance, so the nonelected subject matter is withdrawn from consideration at this time, pursuant to 37 CFR 1.142(b).

***Improper Multiply Dependent Claims***

Claims 5-11 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from another multiple dependent claims. Claims 5-11 each depend in part from claim 3, which is a multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claims not been further treated on the merits in this Office action.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first and second paragraphs of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 12 and 13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds having the formula I, or N-oxides or salts thereof, does not reasonably provide enablement for solvates thereof and solvates of the salts thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

In making the determination of whether certain embodiments of a claimed invention are enabled by the disclosure, the Office relies on the following factors:

- (A) The breadth of the claims;
- (B) The nature of the invention;
- (C) The state of the prior art;
- (D) The level of one of ordinary skill;
- (E) The level of predictability in the art;
- (F) The amount of direction provided by the inventor;
- (G) The existence of working examples; and
- (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

*In re Wands*, 858 F.2d 731,737 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

(A) Insofar as the solvate embodiment of claims 1-4, 12 and 13 is concerned, those claims read on solvates of compounds according to formula I. The scope of the solvates recited in these claims includes solvates of a compound according to formula I, with *any* solvent. The definition of a solvate, taken from the Vippagunta et al reference, cited in section (C), (D), (E) below, is a "crystalline solid adduct[s] containing solvent molecules within the crystal structure, in either stoichiometric or nonstoichiometric proportions, giving rise to unique differences in the physical and pharmaceutical properties of the drug."

(B) The nature of the invention is that of a large family of chemical compounds, specifically, all possible solvates of all chemical compounds comprising said family of compounds.

(C), (D), (E) Solvates, at the time the invention was made, were of course known to chemists of ordinary skill, but not to such an extent that the preparation of specific solvates at will was routine or simple. The following references address the state of the art with respect to crystalline forms of organic compounds, formation of solvates of organic compounds, and the predictability thereof.

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Vippagunta et al, "Crystalline Solids" Advanced Drug Delivery Reviews, vol. 48, pages 3-26 (2001).

and

Gavezzotti, "Are Crystal Structures Predictable?" Accounts of Chemical Research, vol. 27, pages 309-314 (1994).

First, it is evident from both of the references that formation of specific crystalline forms, and more particularly, solvates, is highly unpredictable. See Gavezzotti, page 312, point #8, and Vippagunta et al, page 11, "Prediction of Polymorphs" and page 18 "Prediction of the formation of hydrates and solvates."

Because the formation of solvates is unpredictable, even the relatively high level of skill possessed by one of ordinary skill in the art is not enough to render preparation of solvates routine. Each solvate of each compound must be experimentally prepared (since the conditions necessary for the formation cannot be predicted), wherein all of the factors relevant to each individual compound's ability to crystallize and form solvates are studied. These factors are identified in points #1-7 of the Gavezzotti reference. The preparation of each single claimed solvate represents a significant undertaking in the areas of preparative organic chemistry, physical chemistry, and crystallographic measurements.

It is unknown that the full scope of solvates of compounds of formula I is even possible (see Gavezzotti, page 309, point #1).

(F) Aside from a mention that the invention includes solvates, and solvated salts of the formula I compounds (page 12, lines 12 and 13, for example), no guidance relevant to preparation of solvates is provided in the disclosure.

(G) No working examples, out of the thirteen provided, demonstrate preparation of a solvate. In fact, compounds of the invention are worked up from a variety of solvents

(e.g., ethyl acetate, hexane, water, ether) throughout the working examples, yet no solvate, or even hydrate, is identified.

(H) Each compound of formula I, of which there are thousands, as a solvate with every solvent within the scope of "solvate" generally, of which there are also thousands, providing for many millions of possible combinations, represents the efforts of many individuals over a period of marked in years. Those efforts are potentially inconclusive. For one of ordinary skill in the art to conduct the type of research outlined in Gavezzotti and in Vippagunta et al for preparation of every one of the claimed solvates would be undue. Applicants' right to exclude others from making solvates of compounds according to formula I is unwarranted in light of the lack of any direction as to how one of ordinary skill would do so.

Claims 1-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, several points of indefinite claim language arise; each will be explained –

$X^2$  is defined as being either a bond or " $C_{1-3}alkyl$ ." An alkyl group, as applicants can appreciate, is a monovalent, saturated, hydrocarbon substituent. Since  $X^2$  is a linking moiety, it must be divalent. The proper terminology for such a group as would be contemplated by  $X^2$ , given the imprecise description, would be " $C_{1-3}alkylene$ ." The claim has been examined on the merits as though " $C_{1-3}alkylene$ " were recited in  $X^2$ .

Amendment to replace " $C_{1-3}alkyl$ " with " $C_{1-3}alkylene$ " will not be seen as new matter,

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since it is an obvious error. Corresponding language in the specification must be amended as well.

One of the alternative identities for R<sup>4</sup> is "C<sub>0-3</sub>alkylhydroxy." This term is not an accepted term of art, and is therefore not understood. The specification does not define the term.

Following "C<sub>0-3</sub>alkylhydroxy" in the definition of R<sup>4</sup> is "C<sub>0-3</sub>alkyldimethylamino," which is not understood either. The examiner believes the term could have been intended to represent an quaternary ammonium substituent, but the specification does not provide any basis for giving the term that meaning.

R<sup>3</sup> is defined in the alternative as being "C<sub>0-3</sub>alkyLOC<sub>2-4</sub>alkanol C<sub>1-3</sub>alkanol," which is neither understood by the examiner nor defined in the specification. Page 8 of the specification attempts to define "alkanol," but the definition pertains to compounds *per se*, alcohols, that is. An alcohol is a compound in and of itself; it is not a molecular substituent or radical.

The term "alkanol" appears in claim 2 as well. Claim 2 is therefore further indefinite, in addition to being indefinite for depending from an indefinite base claim for recitation of that term.

Claims 3 and 4 are included in this rejection because those two claims depend from indefinite base claims, 1 and 2, and are therefore indefinite.

#### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

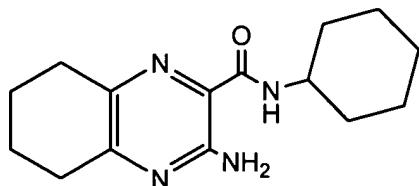
A person shall be entitled to a patent unless –

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(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Keir and MacLennen, "Ethyl Amidinoacetates in the Synthesis of Pyrazines" Journal of the Chemical Society, Perkin Transactions 1, vol. 9, pages 1002-1006 (1978).

On page 1003 of Keir and MacLennon, compound "r" is reported, which is a compound embraced by instant claims 1-3 wherein: Q is a six-membered saturated cycloalkyl ring (cyclohexyl fused to pyrazine); P is a six-membered fully saturated cycloalkyl ring (cyclohexyl); m and n are both equal to zero; X<sup>1</sup> is oxygen; X<sup>2</sup> is a bond; R<sup>2</sup> is hydrogen; R<sup>4</sup> is amino (-NH<sub>2</sub>), or "C<sub>0</sub>alkylamino" as recited in the definition of R<sup>4</sup> in claim 1. The structure of the compound is represented here for applicants' convenience:



#### ***Allowable Subject Matter***

Claims 12 and 13, should the rejection under 35 U.S.C. 112, first paragraph be overcome, would be allowable. Deletion of "solvates or solvates of the salts" would obviate the enablement rejection.

As indicative of the state of the prior art with respect to compounds similar to those according to the instant claims, the examiner cites:

US 6,429,207 (Van Wagenen et al), which discloses some metabotropic glutamate receptor antagonists based on quinoxaline core structure (among other types of compounds) like those according to the invention, but compounds of the Van

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Wagenen et al patent do not include anywhere the carbocyclic portion of the quinoxaline system is partially or fully saturated. In some of the compounds of the Van Wagenen et al patent, the ring corresponding to "P" of formula I in the instant claims is a saturated cycloalkyl ring (compounds 208-210, for example).

US 4,709,052 (Tomioka et al), which discloses compounds for controlling soil diseases. Compound number 201 (col. 41-42) is similar to a compound according to formula I of the instant claims, but the ring corresponding to the "Q" ring of formula I is aromatic in this compound, which is not permitted in formula I. The ring corresponding to "P" is a saturated cycloalkyl ring, however.

US 5,977,108 (Kikuchi et al) discloses retinoid receptor agonists. Example 26 in the Kikuchi et al patent is a compound similar to a compound of the instant claims where the ring corresponding to "Q" is a pyrrolidine ring, substituted with a propyl group; example 88 is similar to compound of the instant invention where "Q" is cyclohexyl; example 89 is similar to a compound of formula I where "Q" is a cyclopentyl ring. In each of these compounds, the moiety corresponding to "P" is a phenyl ring, completely unsaturated.

East German patent (D.D.R.) number 220602 discloses one compound like a compound according to the instant claims, where the "X<sup>1</sup>" position is a sulfur atom, "P" is a cyclohexane ring, but "Q" is a benzo-fused ring (completely unsaturated). An abstract of DD 220602 is provided herewith.

British patent GB 1 308 370 discloses antibiotic compounds having either quinoxaline or benzimidazole core structure. At page 13, in the table, the eighteenth through the twenty-first compounds listed (they are not numbered) are quinoxaline compounds similar to those according to formula I. The ring corresponding to "P" is

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cycloheptyl or cyclohexyl, while "Q," of course, is completely unsaturated, since the compounds are quinoxalines.

Formula I compounds according to the instant claims do not provide for rings "Q" which are aromatic or completely unsaturated.

***Conclusion***

Any inquiry concerning this communication should be directed to Zachary Tucker whose telephone number is (571) 272-0677. The examiner can normally be reached Tuesday-Thursday from 8:00am to 4:30pm or Monday from 6:00am to 1:30pm. If attempts to reach the examiner are unsuccessful, contact the examiner's supervisor, James O. Wilson, at (571) 272-0661.

The fax number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

zt

Zach